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10/080,273	02/19/2002	Peter S. Lu	020054-002310US	6968

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,273	LU ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/22/06, 12/17/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 37-41* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 37, 38, 40, 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/22/03, 1/26/04, 5/3/04, 3/9/04, 6/18/04*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed 5/22/06, and Applicant's amendment filed 12/17/04 are acknowledged and have been entered.

2. Applicant's election with traverse of Group I drawn to a method for screening a compound to determine whether the compound inhibits immune cell signaling, said method comprising identifying a compound that inhibits the interaction between the PDZ protein TIP1 and the PL protein LPAP (claims 1-5), and species of the entire sequence of both said proteins in Applicant's response filed 5/22/06 is acknowledged.

The basis for Applicant's traversal is of record in the said response on pages 5-8, briefly that: there is no statutory basis for requiring restriction within a single claim for restricting modulation to inhibition (Group I) *versus* activation (Group II), for restricting to one PDZ protein and one PDZ ligand protein, that the restriction requirement requires division of a generic claim, the discretionary power to limit one application to one invention is not excuse for refusing to examine a broad generic claim (Applicant cites *In re Weber*), and a Markush-type claim can include independent and distinct inventions.

It is the Examiner's position that:

(1) Inventions of GROUP I and GROUP II are directed to related inventions. The related inventions are distinct if the inventions as claimed do not overlap in scope, *i.e.,* are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, one method detects a compound that inhibits immune cell signaling (GROUP I), the other detects a compound that activates immune cell signaling (GROUP II), two mutually exclusive activities that are not obvious variants of one another. The said methods have a materially different design, *i.e.,* use different ingredients, perform different method steps and have different endpoints, and

(2) With regard to Applicant's argument as to restricting to one PDZ protein and one PDZ ligand protein, that the restriction requirement requires division of a generic claim, the discretionary power to limit one application to one invention is not excuse for refusing to examine a broad generic claim, and that a Markush-type claim can include independent and distinct inventions, it is the Examiner's position that it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship; however, the limitation "PDZ protein" and "PL protein" encompass many different classes of proteins. The instant specification discloses that the term PPDZ domain" refers to protein sequence of about 90 amino acid residues that has homology to PDS-95, DLG and ZO1 and that a PDZ protein contains a PDZ domain (especially paragraph

spanning pages 10-11 and lines 17-19), and that the term "PL protein" refers to a naturally occurring protein that forms a molecular complex with a PDZ domain (especially page 11 at lines 20-21). Evidentiary reference Harris and Lim (J. Cell Science, 2001, 114: 3219-3231, IDS reference) teaches that PDZ proteins domains are small compact globular folds that consist of six β-strands and two α-helices, but there are at least 5-10 general specificity classes, and the question of 'do the 394 different PDZ domains found in humans each recognize a unique set of sequences' will require a large-scale proteomics effort to elucidate the specificities of large sets of interaction domains (especially third full paragraph at column 1 on page 3222). Said reference further teaches such classes include Class I, Class II, and Class II among others, and that their consensus binding sequences are different (especially Table 1). Evidentiary reference Marfatia *et al* (J. Biol. Chem. 1997, 272(39): 24191-24197, IDS reference) teaches that the primary structures of both the PDZ domain and its target peptide govern the specificity as well as the affinity of PDZ domain-mediated interactions (especially column 2 on page 24191). Evidentiary reference WO 00/48002 (IDS reference) teaches that Class I and Class II PDZ domains bind different consensus motifs, and the Class II PDZ domains differ from Class I PDZ domains by formation of a second hydrophobic binding pocket, whereas the Class I PDZ domains contain only one binding pocket (especially page 7 at lines 9-25).

It is the Examiner's position therefore, that the recited PDZ proteins containing a PDZ domain do not have the same structure in common in terms of peptide binding cleft and pockets in said cleft. It is the physicochemical structure of the proteins and their binding sites and subsites (*i.e.,* binding cleft and/or pocket(s)) that are mainly responsible for their function in the claimed relationship, and these structures vary among different classes. It is the Examiner's further position that *In re Weber* made no decision on the propriety of the Markush rejection, and that 121 provides the Commissioner with the authority to promulgate rules designed to restrict an application to one of several claimed methods. 121 provides that the Examiner is authorized to require Applicant to restrict the Application to a single invention, delineating the members of groups of members and state reasons explaining why they are independent and distinct.

Upon reconsideration, the Examiner will examine a method recited in instant claims 1-5, 37, 38, 40 and 41 that read upon the class of PDZ protein domain that TIP1 falls into. It is requested that Applicant disclose which class TIP1 is and which other recited PDZ proteins are encompassed by the same class.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claim 39 (inventions falling into non-elected groups "II") are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-5, 37, 38, 40 and 41 are currently being examined.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP 602.01 and 602.02.

The oath or declaration is defective because: Inventors Seed, Xavier and Irving have not signed the declaration.

4. The abstract of the disclosure is objected to because it contains text that is not part of the abstract paragraph, *i.e.,* "DE 7062664v2." Correction is required. See MPEP § 608.01(b).

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

7. The disclosure is objected to because of the following informalities:

a. The brief description of the drawings discloses Figure 5A-K, however, there are only parts A-I in Figure 5.

b. There are two sets of disparate page numbers on each page of the specification, claims and abstract, *i.e.,* one at the lower left and one at the bottom center of each page.

c. The page of the specification numbered "1" at the lower left hand corner of said page contains a blank underlined space.

Appropriate correction(s) is/are required.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 2-5, 37, 38, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material that is not supported by the specification and claims as originally filed is as follows: (1) The method recited in instant claim 1 wherein said method is for screening a compound to determine whether the compound modulates immune cell signaling, said method comprising contacting an immune cell with a compound that alters binding between a PDZ protein and a PDZ ligand protein (PL) in the cell [*i.e.,* said method step involves contacting with a compound known to alter binding], and (2) determining whether the PDZ protein and/or the PL protein moves into or out of lipid rafts in the plasma membrane of the immune cell, wherein modulation of the movement into or out of lipid rafts indicates the compound modulates immune cell signaling; (3) The method step recited in claims 37 and 38, wherein the determination of movement into and out of lipid rafts includes isolating lipid rafts by density gradient centrifugation, and wherein the determining step is performed before and after addition of the compound, respectively.

Applicant does not point to support for the said claim amendment.

The originally filed disclosure is to: (1) a screening method to determine *if* a compound modulates immune cell signaling, and (2) wherein amount of complex formation in the presence of the [test] compound versus in the absence of the compound is an indication that the compound is a modulator of immune cell signaling, the PDZ and PL proteins having the property of being able to interact with one another to affect the composition and/or distribution of lipid rafts when present in the immune cell [*i.e.,* the determination of movement into or out of lipid rafts was not a method step disclosed in the originally filed specification and claims, but rather of property of the said proteins], (for example, page 4 of the instant specification at lines 10-24) and (3) the disclosure to "lipid rafts" is to a general discussion of lipid rafts on page 1 at lines 20-36 of the instant specification , for example, "The insolubility and buoyant properties of rafts have enabled their isolation via density centrifugation," and to the possibility of "regulating the protein constituents of lipid rafts and their cellular distribution would be a powerful tool in modulating a number of receptor-mediated cellular processes given the role the lipid rafts appear to play in signal transduction" on page 2 of the instant specification at lines 1-23.

10. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method for screening a compound to determine whether the compound modulates immune cell signaling, wherein the compound that alters binding is identified by contacting a PDZ domain polypeptide that *comprises* at least a partial sequence of the PDZ protein and a PL domain polypeptide that *comprises* at least a partial sequence of the PL protein in the presence of the compound.

The instant claim encompasses a screening method wherein the two said polypeptides comprise at least a partial sequence of the PDZ protein and a PL protein, respectively, and wherein the said polypeptides contain undisclosed flanking sequence. There is insufficient disclosure in the specification on such a method.

The instant specification discloses that the term "PDZ-domain polypeptide" refers to a polypeptide containing a PDZ domain, such as a fusion protein including a PDZ domain sequence, a naturally occurring PDZ protein or an isolated PDZ domain peptide (page 11 at lines 17-19). The specification discloses does not disclose the definition of the term "PL domain polypeptide," but does disclose that a "PL protein" or "PDZ Ligand protein" refers to a naturally occurring protein that forms a molecular complex with a PDZ-domain, or to a protein whose carboxy-terminus, when expressed separately from the full length protein, forms such a molecular complex (page 11 at lines 20-23).

Evidentiary reference Harris and Lim (J. Cell Science, 2001, 114: 3219-3231, IDS reference) teaches that PDZ domains recognize specific C-terminal sequence motifs that are usually about five amino acid residues in length, although in some cases, specificity of recognition extends beyond these terminal five residues (page 3220, column 2, last section). The said reference further teaches that some PDZ domains can also recognize internal peptide motifs if presented within a tertiary structure that conformationally mimics a chain terminus (paragraph spanning columns 1 and 2 on page 3222). In addition, the specificity of PDZ domains is primarily determined by the chemical nature of the P_0 and P_{-2} binding pockets (page 3222, column 1 at the first full paragraph). PDZ-complex structures reveal that residues other than the P_{-2} and P_0 residues can also participate in specific interactions with PDZ domain residues that are adjacent to the PDZ peptide binding groove, that these interactions tend to be unique to

individual PDZ domains and are likely to fine tune specificity within each domain class (paragraph spanning pages 3221-3222).

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

11. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, the claimed method for screening a compound to determine whether the compound modulates immune cell signaling, wherein the compound that alters binding is identified by contacting a PDZ domain polypeptide that *comprises* at least a partial sequence of the PDZ protein and a PL domain polypeptide that *comprises* at least a partial sequence of the PL protein in the presence of the compound.

The specification has not enabled the breadth of the claimed invention because the claim encompasses a screening method wherein the two said polypeptides comprise at least a partial sequence of the PDZ protein and a PL protein, respectively, and wherein the said polypeptides contain undisclosed flanking sequence. There is insufficient disclosure in the specification on such a method.

The instant specification discloses that the term "PDZ-domain polypeptide" refers to a polypeptide containing a PDZ domain, such as a fusion protein including a PDZ domain sequence, a naturally occurring PDZ protein or an isolated PDZ domain peptide (page 11 at lines 17-19). The specification discloses does not disclose the definition of the term "PL domain polypeptide," but does disclose that a "PL protein" or "PDZ Ligand protein" refers to a naturally occurring protein that forms a molecular complex with a PDZ-domain, or to a protein whose carboxy-terminus, when expressed separately from the full length protein, forms such a molecular complex (page 11 at lines 20-23).

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chemical nature of the P_0 and P_{-2} binding pockets (page 3222, column 1 at the first full paragraph). PDZ-complex structures reveal that residues other than the P_{-2} and P_0 residues can also participate in specific interactions with PDZ domain residues that are adjacent to the PDZ peptide binding groove, that these interactions tend to be unique to individual PDZ domains and are likely to fine tune specificity within each domain class (paragraph spanning pages 3221-3222). Thus, the evidentiary reference teaches that the conformation of the C-terminus of the PL protein or polypeptide as well as the conformation of the internal sequence is important for binding in the peptide binding cleft of PDZ domains, and conversely, that PDZ domain residues flanking the peptide binding groove may also participate in specific interactions with the PL ligand protein or polypeptide. In addition, the evidentiary reference teaches a specific conformation of the PDZ domains in forming a peptide binding cleft.

The predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain function and properties requires a knowledge of, and guidance with regard to which amino acid residues at which positions in the amino acid sequence, if any are tolerant to modification and which are intolerant to modification, and detailed knowledge of the ways in which the product's structure relates to its function. Evidentiary reference Ngo *et al* (The Protein Folding Problem and Tertiary Structure Prediction, Merz & LeGrand, Birkhauser Boston, pages 491-495, 1994, entire article, especially Section 6, paragraph 1) teaches that the relationship between the sequence of a peptide and its tertiary structure (*i.e.,* its activity) are not well understood and are therefore not predictable.

Because of this lack of guidance and the extended experimentation that would be required to determine which sequences would be acceptable to produce/or retain functional activity, it would require undue experimentation for one of skill in the art to arrive at amino acid sequences for both polypeptides that would have functional activity.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 2 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 2 is indefinite in the recitation of "wherein the compound that alters binding is identified by..." because it is not clear what is meant, *i.e.,* Claim 2 depends upon claim 1 and claim 1 recites contacting an immune cell with a compound that alters

binding (*i.e.*, the compound is already known to alter binding) whereas claim 2 recites a method step wherein the compound that alters binding is identified.

b. Claim 41 is indefinite in the recitation of "monocyte/macrophage" because it is not clear what is meant, *i.e.*, if the cell is a monocyte or a macrophage. A macrophage is a differentiated monocyte.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
July 31, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600